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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,022	05/04/2001	Joseph D. Gold	091/005P	7806

22869 7590 01/16/2004

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	09/849,022	GOLD ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,8-11 and 13-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,8-11 and 13-23* is/are rejected.

7)☒ Claim(s) *17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 10/27/03, has been entered. Claims 4, 7 and 12 are cancelled and claims 13-23 have been added.

Claims 1-3, 5, 6, 8-11 and 13-23 are pending and under current examination.

Claim Objections

Claim 17 is objected to because of the following informalities:

The term "the" is misspelled in part (b) of the claim.

Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The prior rejection of claims 1-3, 5, 6, 8-11 and newly added claims 13-23 is maintained as being provisionally rejected under the judicially created doctrine of

obviousness-type double patenting as being unpatentable over claims 18-22 of copending Application No. 10/039,956. Applicants state that upon allowance of the instant application, Applicant undertakes to cancel corresponding claims in the '956 application, or otherwise address this issue. See p. 6 of the Response. As the instant application has not been found allowable, and no canceling of corresponding claims in the '956 application has been made, the prior rejection is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-3, 8 and 9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 62 and 63 of copending Application No. 09/530,346. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to cell populations comprising undifferentiated primate stem cells. The instant application is directed to methods for producing genetically altered human ES cells by obtaining a culture of human ES cells proliferating on an extracellular matrix, and transfecting the cells with a polynucleotide, and in further embodiments, cell populations comprising undifferentiated human ES cells, some of which have been genetically altered. The '346 claims are directed to cellular compositions comprising undifferentiated primate primordial stem cells proliferating on an extracellular matrix, wherein the cells have been genetically

altered, or are the undifferentiated progeny of genetically altered cells. Accordingly, the instant claims are rendered obvious by the '346 claims, because methods of the instant invention are the only methods that would produce the cells as claimed in the '346 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 6, 8-11 and 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) methods of obtaining or producing genetically altered pluripotent human embryonic stem [ES] cells comprising culturing pluripotent human ES cells in the absence of feeder cells in a culture environment that contains an extracellular matrix and a fibroblast-conditioned medium, and transfecting the human ES cells with a polynucleotide to produce genetically altered pluripotent human ES cells that are undifferentiated and 2) methods for producing genetically altered differentiated cells comprising obtaining a culture comprising pluripotent human ES cells in the absence of feeder cells that contains an extracellular matrix in the absence of feeder cells and a

fibroblast-conditioned medium, transfecting the human ES cells with a polynucleotide to produce genetically altered cells; the specification does not reasonably provide enablement for methods for obtaining or producing genetically altered pPS cells comprising obtaining a culture comprising human ES cells proliferating on an extracellular matrix instead of feeder cells; and transfecting at least some of the cells in the composition with a polynucleotide, thereby producing genetically altered stem cells that are undifferentiated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants have amended the claims to require that the ES cells of the invention be cultured so that they proliferate on an extracellular matrix. See p. 6 of Applicants' Response.

Applicants' amendment is found to be persuasive with regard to the requirement of an extracellular matrix for culturing the hES cells of the instant invention. However, the specification is not found to be enabling with regard to culturing the human ES cells in any type of medium. Particularly, the specification teaches that the traditional culture methods for pluripotent stem cells is on a layer of feeder cells; however, the invention shows an improved system for culturing primate pluripotent stem [pPS] cells in the absence of feeder cells, wherein the role of feeder cells is replaced by supporting the culture on an extracellular matrix *and*

culturing the cells in a conditioned medium. See p. 2, lines 28-30. The specification teaches that a conditioned medium can be used to supply some of the elements provided by feeder cells. See p. 12, lines 36-37. Various cell lines are contemplated to make the conditioned media, for example, mouse embryonic fibroblasts, as well as fibroblast-like cells derived from human embryo cells. See pp. 13-14. The specification teaches that optionally, differentiated cells may be used to condition the medium because they can be further adapted to express a growth factor. These differentiated cells can then be tested to determine if they are suitable for sustaining growth of the pPS cells in feeder-free conditions. See pp. 14-15. The working examples of the specification are drawn to culturing hES cells in an undifferentiated state under feeder-free conditions by culturing in culture wells coated Matrigel and a conditioned nutrient medium obtained from a culture of irradiated primary mouse fibroblasts [mEF]. See Example 1. The specification further teaches the transfection of hES cells in feeder free culture on laminin and mEF conditioned medium. See Example 6.

The claims as broadly written do not specify a type of medium in which the hES cells would be cultured. The state of the art of culturing ES cells is unpredictable. Lim *et al.* [**Proteomics**, 2:1187-1203(2002)] teach the proteome analysis of conditioned medium from mouse embryonic fibroblast feeder layers to characterize the environment that supports the growth of undifferentiated human ES cells, and to identify factors critical for their independent growth. See *Abstract.*

Lim state that, "Despite many years of using mouse embryonic fibroblast cells as feeder support of human ES cells, it is still not clear what these cells for their clients. The interaction between these two cell types might take place *via* factors secreted into the medium or into extracellular matrix as well as through membrane-bound proteins." See p. 1188, 1st ¶. Lim teach that by utilizing proteomic analysis, unexpected results identify many known intracellular proteins, and that further analysis using serum-containing medium in the presence of ES cells, and using other cell types for feeder layers will be required. See p. 1203, 1st ¶, #4.

The instant disclosure teaches that fibroblast-conditioned medium would support undifferentiated growth of human ES cells. However, in light of the state of the art, it would not be predictable that any type of medium would be sufficient to support undifferentiated growth. For example, factors that maintain the hES cells undifferentiated state have yet to be identified, as evidenced by the post-filing art of Lim. Although the specification contemplates utilizing differentiated cells to produce conditioned medium, there are no working examples to show that such medium would be sufficient to maintain hES cells in an undifferentiated state. The specification teaches that further experimentation, such as testing of the media would be required. As specific factors that support undifferentiated growth of hES cells have yet to be identified, it would not be predictable that any media, when used as claimed, would maintain hES cells in an undifferentiated state.

Note further that the enabled scope of the invention is found to be to *pluripotent* human ES cells because the specification fails to teach that human ES cells of the instant invention would give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells, which would be a property of totipotent ES cells.

Accordingly, in view of the unpredictable state of the art of particular media which would be used to culture the hES cells in an undifferentiated state, the lack of working examples to show that any media, other than the exemplified fibroblast-conditioned media, would be sufficient to maintain the hES cells in an undifferentiated state, and the lack of teachings or guidance to show that the ES cells are totipotent, it would have required undue experimentation for one of skill in the art to carry out the claimed methods.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejections of claim 1, 4 and 10 are withdrawn in view of Applicants' arguments and/or amendment(s) to the claims.

Claims 1 and 17, as written, are unclear. The claims recite that the culture of human ES cells proliferating on an extracellular matrix *instead of* feeder cells in part (a) of the claims. The phrase "instead of" is confusing because it is not clear if

the human ES cells were ever on feeder cells. For example, were the cells first cultured on feeders, and then cultured on an extracellular matrix? Claims 2, 3, 5, 6, 22 and 23 depend from claim 1; claims 20 and 21 depend from claim 17.

Claims 13-15 recite the limitation "the undifferentiated pPS cells" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim.

Claims 18 and 19 recite the limitation "the method of claim 8" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6, 8-10, 16 and 17 are rejected under 35 U.S.C. 102(a) as being anticipated by Bodnar *et al.* [WO 99/20740, Reference AH of Applicants' Information Disclosure, filed 12/3/01].

Bodnar teaches methods for culturing primate-derived primordial stem cells. They teach that a primordial stem cell can refer to an embryonic stem cell [see p. 6, section 3.1.10. The primordial stem cells can be cultured in an undifferentiated

state in the presence of a culture media and an extracellular matrix derived from feeder cells. See p. 7, section 3.2.1. Bodnar teaches that the primordial stem cells can be genetically modified to provide cells or tissues for grafting or implantation by introduction of the polynucleotide by positive-negative selection vectors, YACs, etc. The genetically-modified primate-derived primordial stem cells can be differentiated into a different cell type using a particular differentiation promoter. See pp.15-17, Section 3.4.1

Accordingly, Bodnar teaches the claimed invention.

The prior rejection of claims 8-10 under 35 U.S.C. 102(b) as being anticipated by Pedersen is *maintained* for reasons of record.

Applicants argue that the suggestion in the Pedersen reference does not include any of the features provided in the present disclosure that allow embryonic stem cells to be genetically modified while still maintaining the undifferentiated phenotype. Specifically, that Pedersen does not disclose the feeder-free culture method of the invention that allows genetically modified cells to be selected from the culture after transfection. See p. 7 of Applicants' Response.

Applicants' arguments have been considered, but are not found to be persuasive. Pedersen teach pluripotent stem cells derived from early primate embryos, including human embryos. See p. 11, lines 15-26. They teach that the cells of their invention [*i.e.*, pluripotent primate stem cells, including human ES

cells] can be introduced with a wild-type gene, either by homologous or random recombination. See p. 15, lines 24-26. Applicants argue that Pedersen does not disclose the feeder-free conditions of the instant invention. However, the claims merely require that the cell populations comprise undifferentiated human ES cells, wherein some of the cells have been genetically altered. The cells taught by Pedersen anticipate the cells of the instant invention because they fulfill the limitations of the claims.

Accordingly, Pedersen anticipate the claimed invention.

The prior rejection of claims 8-12 under 35 U.S.C. 102(b) by Gearhart *et al.* is withdrawn in view of Applicants' Amendment to the claims with regard to the recitation of *embryonic stem.*

The prior rejection of claim 11 under 35 U.S.C. 102(b) by Dey *et al.* [PNAS, 273:24095-24101 (1998)] is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claim 4 under 35 U.S.C. 103(a) is moot in view of Applicants' cancellation of the claim.

The prior rejection of claims 8 and 9, under 35 U.S.C. 103(a) as being unpatentable over Thomson when taken with Bradley [cited in the previous Office Action] is *maintained* for reasons of record.

Thomson teach human blastocyst-derived pluripotent cell lines that have normal karyotypes, express high levels of telomerase activity, and can proliferate in an undifferentiated state for 4-5 months. See Abstract. In particular, Thomson teach that human embryos were cultured to the blastocyst stage and inner cell masses were isolated and cultured. The resulting cells had morphology similar to that of rhesus monkey ES cells, expressed high levels of telomerase activity and expressed cell surface markes that characterize undifferentiated nonhuman primate ES and human EC cells. See p. 1145, col. 2-3. It was found that the cells produced teratomas after injection into SCID mice, and that the teratomas included cells of the endoderm, mesoderm and ectoderm. See p. 1146, 1st column, 2nd full ¶. Thomson do not teach the transfection of the human pluripotent stem cells with a polynucleotide. However, prior to the time the claimed invention was made, Bradley teach methods of transfecting pluripotent human embryonic stem cells. See col. 8, lines 3-24 and lines 34-44.

Accordingly, in view of the combined teachings of Thomson and Bradley, it would have obvious for one of ordinary skill in the art to transfect the human pluripotent stem cells, as taught by Thomson, by the method taught by Bradley, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as supported by Bradley, that transgenic pluripotent stem cells can be easily selected, for example, if they express a selectable marker. See col. 4, lines 26-38.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 10, 11, 14, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodnar *et al.* [WO 99/20740, Reference AH of Applicants' Information Disclosure, filed 12/3/01] and further in view of Feng *et al.* [JMB, 292:779-785 (1999)].

Bodnar teaches methods for culturing primate-derived primordial stem cells. They teach that a primordial stem cell can refer to an embryonic stem cell [see p. 6, section 3.1.10. The primordial stem cells can be cultured in an undifferentiated state in the presence of a culture media and an extracellular matrix derived from feeder cells. See p. 7, section 3.2.1. Bodnar teaches that the primordial stem cells can be genetically modified to provide cells or tissues for grafting or implantation by

introduction of the polynucleotide by positive-negative selection vectors, YACs, etc. The genetically-modified primate-derived primordial stem cells can be differentiated into a different cell type using a particular differentiation promoter. See pp.15-17, Section 3.4.1.

Bodnar do not teach that at least 25% of the cells have been genetically altered, that the polynucleotide encodes a drug resistance gene, wherein culturing the cells in the presence of the drug to which the genetically altered cells in the population are drug resistant. However, Feng teaches methods of integrating a transgene at a given genomic site in ES cells which have efficiency ranges from 10-50%. See Abstract. The cells were selected by gancyclovir. See p. 785, , 1st column, Cell Culture and Electroporation.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art to use the primordial stem cells cultured on an extracellular matrix, and genetically modify them using the Cre recombinase-mediated cassette exchange protocol, as taught by Feng, to achieve a transfection efficiency of at least 25%, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification because traditional methods of transfecting ES cells have very low efficiency, as stated by Feng. See p. 779, 2nd column; 1st full ¶.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Note: After January 13, 2004, the Examiner may be reached at (571) 272-0736. If the Examiner is unavailable, inquiries may be directed to Deborah Reynolds, SPE of Art Unit 1632, at (571) 272-0734.

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